20 April 2012
EMA/139311/2012
Patient Health Protection

Assessment report for Rasilez

Procedure under Article 20 of **Regulation (EC) No 726/2004**

International Non-proprietary Name: aliskiren

Procedure number: EMEA/H/C/000780/A-20/0063

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

1. Background information on the procedure

On 19 December 2011 the Marketing Authorisation Holder (MAH) for aliskiren containing medicinal products, Novartis Europharm Limited informed the European Medicines Agency of its intention to terminate the ALTITUDE study in patients with type II diabetes at high risk for cardiovascular and renal events following recommendation by the independent Data Monitoring Committee (DMC).

The DMC, further to the outcome (of the seventh safety and second efficacy interim review) of the data from the ALTITUDE study, on 14 December 2011 recommended the study termination concluding that in the study arm of patients receiving aliskiren when added on to conventional treatments for hypertension (either angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB)), patients were unlikely to benefit from treatment. In addition, an increased incidence of non-fatal stroke, renal complications, hyperkalaemia and hypotension in this high-risk study population was observed.

In light of the emerging safety data, there was a need to review all safety data on aliskiren and its impact on the benefit/risk for the approved indication.

Therefore, on 20 December 2011, the European Commission (EC) initiated a procedure under Article 20 of Regulation (EC) No 726/2004 for aliskiren-containing products and, referred the matter to the CHMP. The EC requested the CHMP to assess all the available data and its impact on the risk-benefit balance for aliskiren-containing medicinal products and to give its opinion on measures necessary to ensure the safe and effective use of these medicinal products and whether the marketing authorisations should be maintained, varied, suspended or revoked.

The CHMP firstly considered the safety issue at its extraordinary meeting on 20 to 22 December 2011. Oral explanations were provided by the MAH on 20 December 2011.

A Direct Healthcare Professional Communication (DHPC) and a List of Question to the MAH was adopted by the CHMP on 22 December. An *ad hoc* expert meeting on Cardiovasculars was convened on 13 January 2012 where the MAH gave an Oral Explanation.

The matter was further considered by the CHMP at its meeting in January 2012. Oral explanations were provided by the MAH 16 January 2012. The CHMP adopted a list of outstanding issues on 19 January 2012.

After reviewing all the available data submitted by the MAH to address the concerns discussed, the CHMP adopted an opinion on 16 February 2012.

2. Scientific discussion

2.1. Introduction

Aliskiren is a selective direct inhibitor of human rennin that inhibits the renin-angiotensin system (RAAS) blocking the conversion of angiotensinogen to angiotensin I and decreasing levels of angiotensin I and angiotensin II. Whereas other agents that inhibit the RAAS (ACEi and angiotensin II receptor blockers (ARB)) cause a compensatory rise in plasma rennin activity (PRA), treatment with aliskiren has shown to decrease PRA in hypertensive patients by approximately 50 to 80%.

Aliskiren is approved for the treatment of hypertension in medicinal products containing aliskiren only and in fixed-dose combination medicinal products containing aliskiren in combination with amlodipine, with hydrochlorothiazide, and with amlodipine and hydrochlorothiazide.

The ALTITUDE study (SPP100E2337) was designed to test the hypothesis that the addition of aliskiren to the treatment of type 2 diabetic patients with nephropathy would result in improved cardiovascular and renal outcomes. The study rationale was based on the results of the AVOID study, a phase 2 study which demonstrated an approximately 20 % decrease in urinary albumin creatinine ratio (UACR) in type 2 diabetic patients treated with aliskiren, as compared to placebo. These results suggested a potential beneficial effect of aliskiren on lowering UACR independent of blood pressure (BP) effects. UACR has been extensively supported as a potential surrogate marker for cardiovascular risk in the diabetic population.

Further to the outcome of the seventh safety and second efficacy interim review of the data from the ALTITUDE study, the DMC on the 14 December 2011 recommended the study termination concluding that in the study arm of patients receiving aliskiren when added on to conventional treatments for hypertension (either angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB)), patients were unlikely to benefit from treatment. In addition, an increased incidence of non-fatal stroke, renal complications, hyperkalaemia and hypotension in this high-risk study population was observed.

The CHMP reviewed all data available from the ALTITUDE study, other clinical studies and post marketing data which are hereafter being discussed.

2.2. Clinical aspects

2.2.1. Clinical studies

ALTITUDE study

i. Study design

The ALTITUDE study is a placebo-controlled, double-blind, randomised study designed to investigate the effect of aliskiren on top of optimal cardiovascular treatment including an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) in a specific population of patients with type 2 diabetes and renal impairment with at least one of the following inclusion criteria at randomisation:

- macro-albuminuria (UACR ≥ 200 mg/g) and eGFR ≥ 30 mL/min/1.73m^2
- micro-albuminuria (UACR ≥ 20 mg/g and < 200 mg/g) and a mean estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73m^2 and <60 mL/min/1.73m^2 or

- Cardiovascular disease (CVD) history and a mean eGFR ≥30 mL/min/1.73m^2 and <60 mL/min/1.73m^2 were included.

The primary objective of this study was to determine whether aliskiren, compared to placebo, will delay the occurrence of cardiovascular and/or renal complications when added to conventional treatment in patients with type 2 diabetes at high risk for cardiovascular and renal events.

Occurrence was defined as the time to first event of the following composite primary endpoint: Cardiovascular (CV) death, Resuscitated sudden death, Non-fatal myocardial infarction (MI), Non-fatal stroke, Unplanned hospitalization for heart failure, Onset of end-stage renal disease (ESRD) or renal death, Doubling of baseline serum creatinine concentration, sustained for at least one month, Onset of ESRD is defined as initiation of dialysis, and renal transplantation, or a serum creatinine concentration above 6.0 mg/dL (530 µmol/L).

In total 8606 type 2 diabetic patients were recruited and the patient stratification is reported below in Table 1 below.

Table 1. Patient stratification at randomisation as per investigator

No CV Disease 55.4% of total			**CV Disease 44.5% of total**			
Micro 26.5 % Of No CV disease	Macro 73.4% Of No CV disease		No Alb. 34% Of CV disease	Micro 26% Of CV disease	Macro 39% Of CV disease	
30<eGFR <60 15% Of total	30<eGFR <60 20% Of total	eGFR ≥60 20% of total	30<eGFR <60 15% of total	30<eGFR <60 12% of total	30<eGFR <60 11% of total	eGFR≥60 6% of total

Amongst the total population 55.4% had no previous CV history and 44.5% did have some previous CV disease history.

Of the 55.4% with no CV disease history 26.5% (15% of the total population) had micro albuminuria and 73.4% macro albuminuria (40% of total population).

Of the 44.5% with CV disease history 34% had no albuminuria (15% of total population), 26% had micro albuminuria (11% of total population) and 39% macro albuminuria (17% of total)

Therefore by adding up these numbers for the patients groups with and without CV disease there were overall 15% of patients without albuminuria, 27% with micro albuminuria and 58% with macro albuminuria.

a. Analysis of the interim data of ALTITUDE study

In December 2011 the 7th ALTITUDE Data Monitoring Committee (DMC) met to review the second interim efficacy analysis and the accumulated data related to adverse events, laboratory values and physical status.

A total of 1123 adjudicated primary outcome events, constituting 69% of the projected total primary outcome events, were tabulated. There were 581 (13.6%) patients treated with aliskiren vs. 542 (12.6%) patients treated with placebo who experienced a primary composite endpoint event.

The hazard ratio (aliskiren vs. placebo) for the secondary renal outcome is 0.93 (CI: 0.76, 1.15) suggesting some potential for minimal renal benefit. There is an increase in indices of renal impairment in aliskiren treated patients as evidenced by increased rates of ESRD or renal death (72 in aliskiren vs. 60 in placebo) and SAEs of renal concern (i.e. renal impairment, renal failure acute, renal failure chronic, renal failure with 201 or 4.7% in aliskiren vs. 142 or 3.3% in placebo; p=0.002). There is also an approximately 50% increase in the incidence of SAEs of renal concern within each level of severity in the aliskiren-treated group as compared to placebo.

Based on these results, the study was unlikely to demonstrate a benefit from aliskiren treatment added to standard therapy. The results also suggested a higher incidence of the adverse events of non-fatal stroke, renal complications, hyperkalaemia and hypotension of in this high-risk study population in the aliskiren arm. Given these concerns, the DMC unanimously recommended that all subjects in the ALTITUDE study should cease treatment with aliskiren.

ii. Baseline patient characteristics and concomitant medications

A total of 8,606 patients were randomised in this study at time of termination of the trial. The median age was 65 years, males (68%) and the majority of patients had known diabetes duration of at least 5 years (82%). A history of CV disease was present in 47.9%. The baseline characteristics were: blood pressure 134.7/74.3 mmHg, HbA_{1c} 7.5%, LDL-cholesterol 2.4 mmol/L, haemoglobin 130 g/L, serum creatinine 115 µmmol/L, eGFR 51.7 mL/min/1.73m^2, UACR 198.9 mg/g and frequency of micro-macroalbuminuria 25.7% and 58.2%.

At the time of randomisation and according to protocol, all patients were treated with either an ACE inhibitor or an ARB. At the time of randomisation, 56.6% of subjects were treated with insulin. Biguanides and sulfonylureas were used by 46.2% and 31.9% of subjects respectively (Table 2). ACEis was used by 44.2% of subjects and 55.9% used ARBs. 63.2% of subjects used loop/thiazide diuretics at baseline.

Table 2 CV and anti-diabetic medications at baseline

Medication – n (%)	**Total (N =8606)**
Insulin of any kind	4869 (56.6)
Biguanides	3980 (46.2)
Sulfonylureas	2743 (31.9)
Thiazolidinediones	724 (8.4)
Angiotensin-converting-enzyme (ACE) inhibitor	3807 (44.2)
Angiotensin-II-receptor blocker (ARB)	4815 (55.9)
Beta-blocker	4313 (50.1)
Calcium channel blocker	5267 (61.2)
Loop/thiazide diuretics	5438 (63.2)
Aldosterone receptor blocker	30 (0.3)
Statin	5601 (65.1)
Other lipid lowering agent	1393 (16.2)
Aspirin only	4184 (48.6)
Aspirin or other anti-platelet agent	5380 (62.5)

Primary composite endpoint

The table 3 below includes a summary of the primary and secondary efficacy analyses from the interim analysis.

Table 3 Time-to-event analysis for the primary and secondary composite outcomes and each component outcome based on adjudicated events Randomised Population

				----------(1)----------				
Variable	**aliskiren (N=4283)**	**placebo (N=4296)**	**Total (N=8579)**	**HR**	**95% CI**	**P-value**	**Z-value**	**Information**
Primary composite outcome	581 (13.6%)	542 (12.6%)	1123 (13.1%)	1.09	(0.97, 1.22)	0.1663	1.3843	0.6932
Secondary composite outcome - CV	444 (10.4%)	396 (9.2%)	840 (9.8%)	1.14	(0.99, 1.30)	0.0664		
Secondary composite outcome - renal	166 (3.9%)	180 (4.2%)	346 (4.0%)	0.93	(0.76, 1.15)	0.5178		
Component event (3):								
CV death	179 (4.2%)	162 (3.8%)	341 (4.0%)	1.12	(0.90, 1.38)	0.3110		
Resuscitated sudden death	13 (0.3%)	8 (0.2%)	21 (0.2%)	1.64	(0.68, 3.95)	0.2737		
Non-fatal MI	90 (2.1%)	88 (2.0%)	178 (2.1%)	1.03	(0.77, 1.39)	0.8302		
Non-fatal stroke	112 (2.6%)	85 (2.0%)	197 (2.3%)	1.34	(1.01, 1.77)	0.0439		
Unplanned hospitalization for heart failure	150 (3.5%)	155 (3.6%)	305 (3.6%)	0.98	(0.78, 1.23)	0.8716		
Onset of ESRD/renal death	72 (1.7%)	60 (1.4%)	132 (1.5%)	1.22	(0.87, 1.72)	0.2518		
Doubling of baseline serum creatinine (2)	141 (3.3%)	159 (3.7%)	300 (3.5%)	0.90	(0.71, 1.12)	0.3431		
Death from any cause (4)	297 (6.9%)	277 (6.4%)	574 (6.7%)	1.08	(0.92, 1.27)	0.3661		

(1) All estimates are based on Cox regression models stratified by CV disease history and UACR (≥200mg/g) with treatment assignment as a covariate. Hazard ratio (HR) is exponential of parameter estimate. Z-value is the Wald test statistic, calculated as parameter estimate divided by standard error. The upper boundary is 2.4547 and the nominal α-level is 0.0140. Information is defined the total number of patients with primary events in the interim analysis divided by 1620.

(2) Event date is the first doubling date (event confirmed at least one month after the first doubling date).

(3) Each component event and all death are analyzed independently. The first of each type of event for each subject is counted regardless of whether it was the first event for that subject.

(4) Deaths submitted for adjudication are included.

A total of 1123 patients experience a primary composite endpoint as previously defined and the hazard ratio (aliskiren/placebo) for the primary composite endpoint was 1.09 (95% CI 0.97-1.22).

The Kaplan-Meier curves for the aliskiren-treated (A) and the placebo-treated (B) subjects for the primary composite endpoint do not separate before approximately 15-18 months.

iii. Cardiovascular (CV) composite endpoint

The table below includes a summary of the primary and secondary efficacy analyses from the DMC report augmented with 2 rows “All Stroke” and “All MI”, including fatal strokes and fatal MIs.

Table 4 Time-to-event analysis for the primary and secondary composite outcomes and each component outcome based on adjudicated events including stroke (fatal and non-fatal) and MI (fatal and non-fatal): Overall (by treatment)

				----------(1)----------	
Variable	**Aliskiren (N=4283)**	**Placebo (N=4296)**	**Total (N=8579)**	**HR**	**95% CI**
Primary composite outcome	581 (13.6%)	542 (12.6%)	1123 (13.1%)	1.09	(0.97, 1.22)
Secondary composite outcome - CV	444 (10.4%)	396 (9.2%)	840 (9.8%)	1.14	(0.99, 1.30)
Secondary composite outcome - renal	166 (3.9%)	180 (4.2%)	346 (4.0%)	0.93	(0.76, 1.15)
Component event (3):					
CV death	179 (4.2%)	162 (3.8%)	341 (4.0%)	1.12	(0.90, 1.38)
Resuscitated sudden death	13 (0.3%)	8 (0.2%)	21 (0.2%)	1.64	(0.68, 3.95)
Non-fatal MI	90 (2.1%)	88 (2.0%)	178 (2.1%)	1.03	(0.77, 1.39)
Non-fatal stroke	112 (2.6%)	85 (2.0%)	197 (2.3%)	1.34	(1.01, 1.77)
Unplanned hospitalization for heart failure	150 (3.5%)	155 (3.6%)	305 (3.6%)	0.98	(0.78, 1.23)
Onset of ESRD/renal death	72 (1.7%)	60 (1.4%)	132 (1.5%)	1.22	(0.87, 1.72)
Doubling of baseline serum creatinine (2)	141 (3.3%)	159 (3.7%)	300 (3.5%)	0.90	(0.71, 1.12)
Death from any cause (4)	297 (6.9%)	277 (6.4%)	574 (6.7%)	1.08	(0.92, 1.27)
All Stroke (including fatal stroke)	114 (2.7%)	86 (2.0%)	200 (2.3%)	1.34	(1.02, 1.78)
All MI (including fatal MI)	95 (2.2%)	92 (2.1%)	187 (2.2%)	1.04	(0.78, 1.39)

(1) All estimates are based on Cox regression models with treatment assignment as a covariate. Hazard ratio (HR) is exponential of parameter estimate.

(2) Event date is the first doubling date (event confirmed at least one month after the first doubling date).

(3) Each component event and all death are analyzed independently.

(4) Events submitted for adjudication are included.

A total of 840 patients experienced a secondary composite cardiovascular endpoint. The CV composite endpoint is defined as the first occurrence of CV death, resuscitated sudden death, non-fatal MI, non-fatal stroke, or unplanned hospitalization for heart failure (HF).

The hazard ratio (aliskiren/placebo) for the secondary CV composite endpoint was 1.14 (95% CI 0.99-1.30).

Kaplan-Meier curves for aliskiren and placebo treatment groups started to diverge for the secondary CV composite after approximately 1.5 years

iv. Renal composite endpoint

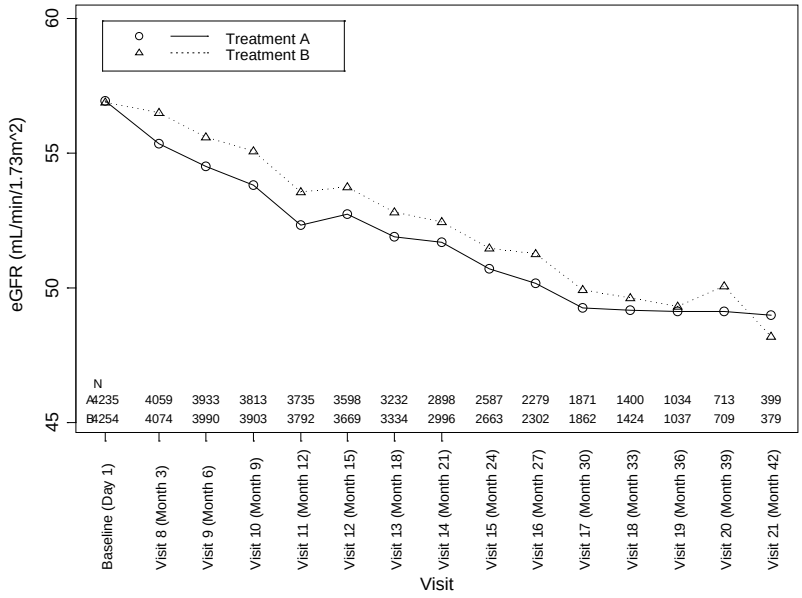
The previous table includes a summary of the primary and secondary efficacy analyses from the interim analysis with the renal endpoints in addition to the CV endpoint already described. For the onset of ESRD/renal death 72 (1.7%) of patients in the aliskiren group experienced an adjudicated endpoint vs. 60 (1.4%) in the placebo group with a hazard ratio 1.22 (95% CI 0.87-1.72). For the doubling of serum creatinine there was a slight benefit in favour of aliskiren with 141 patients on aliskiren reaching the endpoint (3.3%) vs. 159 (3.7%) with placebo, hazard ratio 0.90 (95% CI 0.71-1.12).

A late separation of the two Kaplan-Meier curves was observed between 20-24 months for the renal composite endpoint in favour of aliskiren.

Change in UACR and eGFR

The UACR continuously goes up over the course of the study in the placebo group as opposed to dropping and remaining stable in the aliskiren group.The effect of aliskiren on top of ACE inhibitor or ARB treatment in the ALTITUDE trial shows a 20% difference as compared to placebo..

Figure 1 eGFR over time



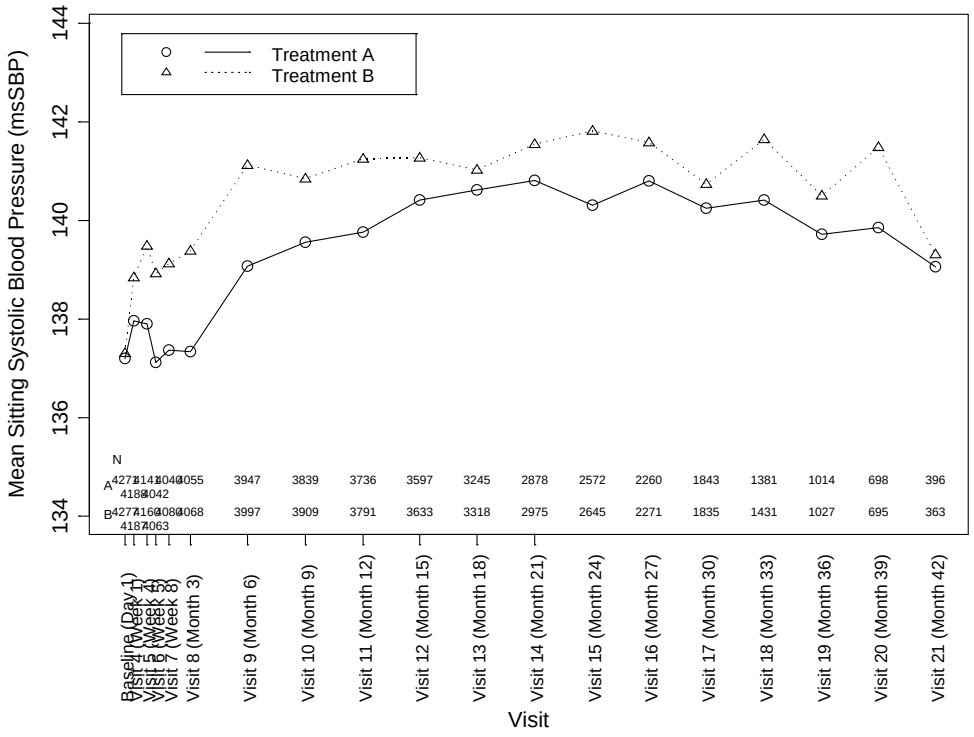
Treatment A = aliskiren; treatment B = placebo

The figure above shows the changes in eGFR during the course of the study for the two treatment groups. As expected there was a greater initial drop in eGFR with aliskiren corresponding to an acute hemodynamic effect at the glomerular level. No long-term benefit was demonstrated because eGFR continued to decline in both the placebo and aliskiren treatment groups over time.

v. Change in Blood Pressure (BP)

The figure 2 below shows the change in mean sitting systolic blood pressure (msSBP) during the course of the study. After an initial drop, blood pressure steadily increased by 2-3 mmHg in both treatment groups although the mean BP was approximately 1-1.5 mmHg lower for the aliskiren treatment group over the time course of the study.

Figure 2 msSBP over time



Treatment A = aliskiren; treatment B = placebo

b. Safety Results from ALTITUDE Study

Serious renal failure events (renal failure, renal failure acute, renal failure chronic, renal impairment)

The following table 4 is summarising the event of serious renal failure in the interim analysis report.

Table 4 Serious Renal Failure Randomised Population

		Aliskiren (N=4283)	Placebo (N=4296)	Total (N=8579)
Any serious renal failure event		**201 (4.7%)**	**142 (3.3%)**	**343 (4.0%)**
Preferred Term	Renal impairment	71 (1.7%)	48 (1.1%)	119 (1.4%)
	Renal failure acute	59 (1.4%)	48 (1.1%)	107 (1.2%)
	Renal failure chronic	63 (1.5%)	35 (0.8%)	98 (1.1%)
	Renal failure	39 (0.9%)	21 (0.5%)	60 (0.7%)

As indicated in the table above, a total of 343 patients experienced a serious renal failure event defined as serious adverse events (SAEs) with preferred terms as indicated in the table. These events have not been adjudicated.

Cox regression analyses were performed for this endpoint. There was a statistically significant difference between treatment groups. Treatment effect adjusted for all specified covariates in a multivariate Cox regression model was: HR (aliskiren vs. placebo) =1.44 (95% CI 1.15-1.81; p=0.0018).

The renal SAEs were assessed for severity and the results are presented in the following table 5.

Table 5 Worst severity of renal SAEs

		Aliskiren (N=4283)	Placebo (N=4296)	Total (N=8579)
Worst Renal Score	1	51 (1.2%)	36 (0.8%)	87 (1.0%)
	2	36 (0.8%)	26 (0.6%)	62 (0.7%)
	3	1 (<0.1%)	0 (0.0%)	1 (<0.1%)
	4	51 (1.2%)	35 (0.8%)	86 (1.0%)
	5	29 (0.7%)	18 (0.4%)	47 (0.5%)
	6	3 (0.1%)	1 (<0.1%)	4 (<0.1%)

Adverse events of concern - namely hypotension, stroke, hyperkalaemia and renal failure are presented in the table below. Overall there was an increase in adverse events in the aliskiren group for all categories. When looking at the stroke incidence there were more strokes of an ischemic nature whereas the strokes of hemorrhagic nature were less frequent. Furthermore, there was an increase in the ischemic stokes in the aliskiren group as compared to placebo (table 6).

Table 6 Adverse Events of Concern: Overall (by treatment) Randomised Population

	Aliskiren (N=4283)	Placebo (N=4296)	Total (N=8579)
CNS and Hypotensive events	**790 (18.4%)**	**628 (14.6%)**	**1418 (16.5%)**
Circulatory collapse	7 (0.2%)	4 (0.1%)	11 (0.1%)
Depressed level of consciousness	3 (0.1%)	1 (<0.1%)	4 (<0.1%)
Dizziness	302 (7.1%)	285 (6.6%)	587 (6.8%)
Hypotension	494 (11.5%)	319 (7.4%)	813 (9.5%)
Loss of consciousness	10 (0.2%)	8 (0.2%)	18 (0.2%)
Orthostatic hypotension	50 (1.2%)	45 (1.0%)	95 (1.1%)
Shock	1 (<0.1%)	0 (0.0%)	1 (<0.1%)
Syncope	63 (1.5%)	74 (1.7%)	137 (1.6%)
Hemorrhagic Stroke	**20 (0.5%)**	**17 (0.4%)**	**37 (0.4%)**
Brain stem haemorrhage	2 (<0.1%)	0 (0.0%)	2 (<0.1%)
Cerebellar haemorrhage	1 (<0.1%)	0 (0.0%)	1 (<0.1%)
Cerebral haemorrhage	8 (0.2%)	8 (0.2%)	16 (0.2%)
Haemorrhage intracranial	0 (0.0%)	2 (<0.1%)	2 (<0.1%)
Haemorrhagic stroke	4 (0.1%)	4 (0.1%)	8 (0.1%)
Subarachnoid haemorrhage	5 (0.1%)	3 (0.1%)	8 (0.1%)
Hyperkalaemia	1579 (36.9%)	1165 (27.1%)	2744 (32.0%)
Ischemic Stroke	**142 (3.3%)**	**112 (2.6%)**	**254 (3.0%)**
Basal ganglia infarction	2 (<0.1%)	0 (0.0%)	2 (<0.1%)
Basilar artery occlusion	0 (0.0%)	1 (<0.1%)	1 (<0.1%)
Brain stem infarction	4 (0.1%)	0 (0.0%)	4 (<0.1%)
Cerebellar infarction	1 (<0.1%)	2 (<0.1%)	3 (<0.1%)
Cerebral infarction	35 (0.8%)	33 (0.8%)	68 (0.8%)
Cerebral thrombosis	1 (<0.1%)	0 (0.0%)	1 (<0.1%)
Cerebrovascular accident	88 (2.1%)	63 (1.5%)	151 (1.8%)
Embolic stroke	1 (<0.1%)	1 (<0.1%)	2 (<0.1%)
Ischaemic cerebral infarction	2 (<0.1%)	0 (0.0%)	2 (<0.1%)

	Aliskiren (N=4283)	Placebo (N=4296)	Total (N=8579)
Lacunar infarction	12 (0.3%)	17 (0.4%)	29 (0.3%)
Thalamic infarction	2 (<0.1%)	0 (0.0%)	2 (<0.1%)
Thrombotic stroke	0 (0.0%)	1 (<0.1%)	1 (<0.1%)
Renal	**532 (12.4%)**	**447 (10.4%)**	**979 (11.4%)**
Renal failure	79 (1.8%)	52 (1.2%)	131 (1.5%)
Renal failure acute	83 (1.9%)	65 (1.5%)	148 (1.7%)
Renal failure chronic	88 (2.1%)	58 (1.4%)	146 (1.7%)
Renal impairment	366 (8.5%)	313 (7.3%)	679 (7.9%)

c. Additional subgroup analyses of ALTITUDE study

Comparison of patients with or without CV events

Patient Characteristics

Out of the total of 4283 patients in the aliskiren treatment group, 444 patients (10.4 %) suffered a cardiovascular (CV) event. Of the 4296 patients in the placebo arm, 396 (9.2%) patients experienced a CV event.

Patients who suffered a CV event over the course of the study tended to be older with a mean age of 67.1 (SD 9.1) as compared to the group of patients who did not have a CV event with a mean age of 64.3 (SD 9.6) in the aliskiren arm. The incidence of CV events is higher in patients ≥ 65, and ≥ 75 years old. A similar finding is observed in the placebo arm.

The incidence of CV events observed is higher in males as compared to females both in the aliskiren and in the placebo arm.

No major imbalances are observed with regard to baseline demographic characteristics between patients with CV events vs. patients without CV events in the aliskiren arm.

With regards to medical history, the sub-group of patients that experienced a CV event during the course of the trial included more patients with a history of CV event prior to entry in the study (e.g history of heart failure (HF) and prior hospitalization, stenosis ≥ 50 % in a major epicardial coronary artery, prior unstable angina, and stable angina, prior Coronary Artery Bypass Grafting (CABG), prior hospitalization for MI, stroke, transitory ischemic attack, etc.) as compared to those patients that did not suffer a CV event in the aliskiren arm. This trend is also observed in the placebo arm, confirming the existence of a higher CV risk in patients who have a history of CV events irrespective of the treatment assignment.

With regard to diabetes history, those patients that suffered a CV event compared to patients without CV events, tended to have a longer history of the disease (> than 5 years) 86.5 % vs. 81.8 % in the aliskiren treated group as well a higher family history of premature atherosclerotic events 20 % vs. 15 %.

The difference observed in the placebo group is slightly less marked with regard to the length of the disease (history of diabetes >5 years) 83.3 % vs. 82.3%, as well as the history of premature atherosclerotic events 16.4 % vs. 15 %.

No major differences are observed with regard to the previous renal history at baseline in both the aliskiren and placebo arms.

Medication at baseline

Overall, the use of relevant antihypertensive and anti-diabetic drugs at baseline are equally distributed between aliskiren and placebo treated patients. The proportion of patient treated with ACEIs and ARBs is 45 % and 55 % in the aliskiren arm and 43.4% and 56.8 % in the placebo arm respectively. Patients on aliskiren had a lower use of statins compared to placebo (63.7 % vs. 66.3%). With regards to the use of ACE inhibitors and ARBs, there is a greater use of ACEIs in patients who had a CV end point in both groups (aliskiren and placebo) 51.9 % and 50.3 % respectively compared to those who did not have a CV event 44.2% and 42.8%.

With regards to the use of anti-diabetic drugs in patients with CV events, there is a higher frequency in the use of insulin as compared to those patients that did not have an event, 65.3 % vs. 53.0 % in aliskiren treated patients. This is also observed in the placebo treated patients 57.8 % vs. 53.4 %.

A similar distribution is observed in the group of patients that had a stroke in the aliskiren and in the placebo groups.

Changes in Blood Pressure

Overall, the systolic BP (SBP) in patients who had a CV event tended to be stable over time. The mean SBP (mSBP) was comparable between the aliskiren and placebo arms. In the aliskiren arm, the mean SBP at baseline is 140.1 mmHg vs. 140.7 mmHg at the last visit (change +0.59). In the population treated with aliskiren who did not experience a CV event, the SBP tended to be lower at baseline with mean 136.9 mmHg vs. 140 .5 mmHg at the last visit (change +3.58 mmHg). No major fluctuations are observed over time during the course of the study.

A similar trend is observed in the placebo group for msSBP in patients that suffered a CV event. In this group the mSBP at baseline is 138.6 mmHg vs. 139.7 mmHg (change +1.10 mmHg). In the population without events, the baseline mSBP is 137.2 mmHg vs. 141.6 mmHg (change +4.40 mmHg).

No major imbalances in demographic characteristics that may identify patients at increased risk for renal events within the ALTITUDE study cohort have been identified. The incidence of cardiovascular events was greater in men compared to women but this difference is explained by the mean age of patients included in the study as cardiovascular events are greater in men than in women until the age of 70-75 years.

The use of background therapy was similar in patients receiving aliskiren or placebo.

Changes in UACR and eGFR

With regard to the renal function, eGFR declined over time in both arms but it was more pronounced in the aliskiren treated population. With regards to the UACR, the aliskiren treated patients had a reduction of the UACR over time of about 20 % as compared to the placebo group.

Review of Stroke (fatal and non-fatal)

A total of 200 patients experienced an adjudicated stroke (fatal or non-fatal). The hazard ratio (aliskiren/placebo) for all strokes was 1.34 (95% CI 1.02-1.78). The inclusion of fatal strokes in the analysis increased the number of events by 3, compared to the non-fatal event analysis.

The treatment effect adjusted for 25 covariates in a multivariate Cox regression model is similar to the unadjusted treatment effect: HR (aliskiren vs. placebo) =1.35 (95% CI 1.01-1.82; p=0.0461). Kaplan-Meier curves for treatment groups aliskiren (A) and placebo (B) started to diverge after approximately 1.5 years.

A statistically significant treatment by covariate interaction (p-value < 5% in univariate Cox-regression) has been identified, for baseline Calcium Channel Blocker use (p=0.0489). The hazard ratio for treatment A (aliskiren) vs treatment B (placebo) was 1.60 (95% CI 1.15-2.24) for patients who

received Calcium Channel Blocker at baseline, while it was 0.85 (95% CI 0.50-1.45) when patients did not receive Calcium Channel Blocker at baseline.

The other factor suggesting covariate by treatment interaction (p-value < 10% in univariate Cox-regression) was prior hospitalization for stroke (relatively smaller hazard ratio aliskiren/placebo for patients with prior hospitalization for stroke; p=0.0957).

Hypertension

A slightly higher incidence of history of hypertension was observed in the aliskiren treated patients who had a stroke (97%), as compared to the placebo group with stroke (95%), which was not observed in the patients who did not have a stroke. No relevant differences were observed in the time since hypertension diagnosis.

Hypotension and hypotension related events

An increased incidence of hypotensive effects (collapse, hypotension, loss of consciousness, orthostatic hypotension, shock, syncope) was observed in the aliskiren treatment group for both patients with and without stroke (18.4% and 19.3%, respectively) versus the placebo group (14.6% and 14.0% respectively).

Table 7 Hypotension related adverse events

	Did Not Have a Stroke (Including Fatal) Treatment A (N=4169)	Did Not Have a Stroke (Including Fatal) Treatment B (N=4210)	Had a Stroke (Including Fatal) Treatment A (N=114)	Had a Stroke (Including Fatal) Treatment B (N=86)
CNS and Hypotensive events	768 (18.4%)	616 (14.6%)	22 (19.3%)	12 (14.0%)
Circulatory collapse	7 (0.2%)	4 (0.1%)	0 (0.0%)	0 (0.0%)
Depressed level of consciousness	2 (<0.1%)	1 (<0.1%)	1 (0.9%)	0 (0.0%)
Dizziness	292 (7.0%)	278 (6.6%)	10 (8.8%)	7 (8.1%)
Hypotension	481 (11.5%)	315 (7.5%)	13 (11.4%)	4 (4.7%)
Loss of consciousness	10 (0.2%)	8 (0.2%)	0 (0.0%)	0 (0.0%)
Orthostatic hypotension	50 (1.2%)	44 (1.0%)	0 (0.0%)	1 (1.2%)
Shock	1 (<0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Syncope	61 (1.5%)	72 (1.7%)	2 (1.8%)	2 (2.3%)

Orthostatic hypotension was not observed in the patients on aliskiren who had a stroke (as compared to 1 patient in the placebo group with stroke), however, it occurred more often in the aliskiren treatment group who did not have a stroke compared to placebo (1.2% versus 1.0%, respectively).

Hypotension occurred much more frequently in the aliskiren group for both patients with and without stroke (11.5% and 11.4% respectively), as compared to placebo (7.5% and 4.7% respectively).

Prior hospitalisation for MI, stroke, or a prior Percutaneous Coronary Intervention (PCI)

In the overall study population there is a slight numerical imbalance in favour of the aliskiren group in the following categories of medical history at baseline prior stroke 439 (10.2 %) vs. 410 (9.5 %), prior transient ischemic attack (TIA) 179 (4.2%) vs. 173 (4%), known carotid artery stenosis 282 (6.6%) vs. 275 (6.4 %) and prior carotid revascularization (protective factor) 78 (1.8 %) vs. 99 (2.3%).

An increased incidence of prior atrial fibrillation (AF) was observed in the aliskiren treatment group with stroke (7.9%) versus the placebo group with stroke (7.0%), however, for both groups this was lower than in the patients who did not have a stroke (8.9% and 8.2%, respectively).

An increased incidence of prior PCI was observed in the aliskiren treatment group with stroke (18%) versus the placebo group with stroke (9%). This was also higher than in the patients who did not have a stroke in the aliskiren arm but was lower in the placebo arm (14% and 15%, respectively).

An increased incidence of prior CABG was observed in the aliskiren treatment group with stroke (13%) versus the placebo group with stroke (11%). This was also higher than in the patients who did not have a stroke in the aliskiren arm but was lower in the placebo arm (12% in both treatment groups).

An increased incidence of prior hospitalisation for MI was observed in the aliskiren treatment group with stroke (22%) versus the placebo group with stroke (13%). This was also higher than in the patients who did not have a stroke in the aliskiren arm but was lower in the placebo arm (16% and 17%, respectively).

A lower incidence of prior hospitalisation for stroke was observed in the aliskiren treatment group with stroke (18%) versus the placebo group (27%). The incidence of prior hospitalization for stroke was higher in patients that have a stroke than in patient that did not have a stroke (10% and 9%, respectively).

A lower incidence of prior transient ischemic attack (TIA) was observed in the aliskiren treatment group with stroke (8%) versus the placebo group (9%). This incidence of prior TIA was higher in patients which experience a stroke than in the patients who did not have a stroke (4% in both treatment groups).

Peripheral vascular disease as evidence for atherosclerosis

A higher incidence of intermittent claudication was observed in the aliskiren treatment group with stroke (11%) versus the placebo group with stroke (8%). The incidence in the placebo group with stroke was similar to the incidence in the patients who did not have a stroke and the incidence in the aliskiren group with stroke was higher than in the patients who did not have a stroke (8% in both treatment groups).

A higher incidence of lower limb stenosis as documented by imaging was observed in the aliskiren treatment group with stroke (6%) versus the placebo group (5%). The incidence in the placebo group with stroke was similar as in the patients who did not have a stroke and the incidence in the aliskiren group with stroke was higher than in the patients who did not have a stroke (5% in both treatment groups).

A higher incidence of prior or current foot ulcers was observed in the aliskiren treatment group with stroke (11%) versus the placebo group (9%). This incidence of prior or current foot ulcers was higher in patients which experience a stroke than in the patients who did not have a stroke (9% and 8%, respectively).

Renal disease

Patients who had a stroke (either on aliskiren or placebo treatment) more often had a history of renal disease as compared to patients without stroke (84% and 83% for aliskiren versus 77% and 78 for placebo).

Diabetes

A higher incidence of type 2 diabetes was diagnosed >5 years in the aliskiren treatment group with stroke (87%) versus the placebo group (84%). This was both higher than in the patients who did not have a stroke (82% in both treatment groups).

Other risk factors

No differences were observed for congestive heart failure, prior hospitalization for chronic heart failure (CHF), stenosis > 50% in at least one major epicardial coronary artery, stable angina pectoris, prior unstable angina pectoris, current Canadian cardiovascular Society (CCS) class, known carotid artery stenosis, prior carotid artery revascularization, known renal artery stenosis, prior lower limb revascularisation, clinically significant valvular heart disease, prior atrial fibrillation, cardioverter defibrillator or pacemaker implanted, second or third degree heart block, life-threatening or uncontrolled arrhythmia, or family history of premature atherosclerotic events in both arms.

Baseline concomitant medications and use of concomitant medications during the study

Cardiovascular medications

ACE inhibitors, ARBs, antiplatelets, and beta-blockers (BBs) were equally used within each treatment group for both patients who had a stroke and did not have a stroke.

A larger number of patients on aliskiren with a stroke were also using a calcium channel blockers (CCB) (78%), as compared to patients on aliskiren without stroke (61%), patients on placebo with stroke (65%), and patients on placebo without stroke (61%). Data are not available on any medication changes on-therapy.

After visit 11 (12 months) for both treatment arms there was increased use of anti-platelets in patients with stroke as compared to patients who did not have a stroke.

Anti-diabetic medications

Sulfonylureas were equally used within each treatment group for patients who had a stroke and those who did not have a stroke. However, fewer patients with a stroke (either on aliskiren or on placebo) used insulin (54% aliskiren with stroke, 54% placebo with stroke) as compared to patients without a stroke (65% aliskiren without stroke, 61% placebo without stroke).

Observed changes from baseline

Baseline mean sitting systolic blood pressure and changes from baseline

Baseline msSBP in patients in the stroke group on aliskiren was 142.6 mmHg, which is higher than in the stroke group on placebo (137.8 mmHg). Both were higher than in patients who did not have a stroke (aliskiren 137.1 mmHg and placebo 137.3 mmHg, respectively).

In patients with stroke on aliskiren, msSBP increased during a time period of 12 months to the maximum msSBP of 149.8 mmHg, which is an increase of 6.86 mmHg over baseline (142.94 mmHg), after which msSBP dropped again. However, in patients with stroke on placebo, msSBP increased during a time period of 3 months to the maximum msSBP of 145.3 mmHg, which is an increase of 8.66 mmHg over baseline (136.64 mmHg). Therefore, patients with stroke on aliskiren started with a higher msSBP, had an increase in msSBP over a longer period of time, and had a remaining increased msSBP after 24 months when compared to the patients on placebo.

In patients without stroke on aliskiren, msSBP gradually increased over a time period of 21 months to the maximum msSBP of 140.6 mmHg, which is an increase of 3.57 mmHg over baseline. In patients without stroke on placebo, msSBP gradually increased over a time period of 24 months to the maximum msSBP of 141.6 mmHg, which is an increase of 4.46 mmHg over baseline. Thus, patients without stroke had a much more gradual increase in msSBP over time as compared to patients with a stroke.

Changes in UACR

Baseline mean UACR in patients in the stroke group on aliskiren was 1145 mg/g, which is slightly lower than in patients on placebo in the stroke group (1243 mg/g). Both were much higher than in patients who did not have a stroke (aliskiren 716 mg/g and placebo 723 mg/g, respectively).

In patients with stroke on aliskiren, mean UACR increased during a time period of 24 months to the maximum mean UACR of 1398 mg/g, after which mean UACR dropped again. A similar pattern was seen in patients with stroke on placebo; mean UACR increased during a time period of 24 months to the maximum mean UACR of 1282 mg/g.

In patients without stroke on aliskiren, mean UACR gradually increased over a time period of 18 months to the maximum mean UACR of 759 mg/g. In patients without stroke on placebo, mean UACR gradually increased over a time period of 24 months to the maximum mean UACR of 805 mg/g mmHg.

Therefore, in patients with stroke on aliskiren, baseline UACR and changes from baseline UACR are comparable to those observed in the patients on placebo, and both are much higher than those observed in patients who did not have a stroke (both aliskiren and placebo treatment groups).

Changes in eGFR

Baseline mean eGFR in patients in the stroke group on aliskiren was 52 mL/min/1.73m^2, which is lower than in patients on placebo in the stroke group (59.5 mL/min/1.73 m^2). It was also lower than in patients who did not have a stroke for both arms (57 mL/min/1.73 m^2 in both treatment groups).

In patients with stroke on aliskiren, mean eGFR decreased during a time period of 24 months to the minimum mean eGFR of 45 mL/min/1.73 m^2, which is a decrease of 11.41 mL/min/1.73 m^2 below baseline (56.41 mL/min/1.73 m^2), after which mean eGFR increased again. However, in patients with stroke on placebo, mean eGFR decreased during a time period of 33 months to the minimum mean eGFR of 51 mL/min/1.73 m^2, which is a decrease of 17 mL/min/1.73 m^2 below baseline (56.41 mL/min/1.73 m^2). Therefore, patients with stroke on aliskiren started with a lower mean eGFR, had a decrease in mean eGFR over a shorter period of time, and had a remaining lower mean eGFR after 39 months when compared to the patients on placebo who had a stroke.

In patients without stroke on aliskiren or placebo, mean eGFR gradually decreased over a time period of 36-39 months to the minimum mean eGFR of 47 mL/min/1.73 m^2 (both treatment groups), which is an decrease of 7-8 mL/min/1.73 m^2 under baseline. Thus, patients without stroke had a much less pronounced decrease in mean eGFR over time as compared to patients with a stroke in both arms.

d. Other on-going aliskiren studies

There are four additional ongoing aliskiren studies in adult patients which include data monitoring committees to oversee patient safety. The four trials are ATMOSPHERE (SPP100F2301), ASTRONAUT (SPP100A2368) in chronic and acute heart failure respectively, APOLLO (SPP100G2301) in elderly hypertensive patients and the IVUS study AQUARIUS (SPP100A2366) in patients with coronary artery disease. The DMCs of all these 4 studies were provided with the preliminary analysis report of the ALTITUDE data and related DMC conclusions and were requested to provide a recommendation on whether their studies should continue based upon the results of ALTITUDE. All on going studies were recommended to be continued. The CHMP is in agreement.

e. Other completed aliskiren studies

In addition to the hypertension studies, 5 clinical trials with aliskiren-based therapy that were conducted in other patient populations were included in this review. All studies included in this review have previously been submitted to the CHMP.

Table 8. Aliskiren studies in other patient populations

Clinical studies	Patient population	Treatment
ASPIRE (SPP100A2340/E1)	AMI (within 7-42 days) associated with LV systolic dysfunction.	Aliskiren or placebo on top of standard therapy
ALLAY (SPP100A2316)	Essential hypertension and LVH	Aliskiren, losartan or aliskiren/losartan combination
ALOFT (SPP100A2313)	Essential hypertension and stable heart failure and a baseline BNP >100 pg/ml (28.9 pmol/L)	Aliskiren or placebo on top of standard therapy
AVANT GARDE (SPP100A2347)	Post acute coronary syndromes (ACS) with elevated levels of natriuretic peptides (NT-proBNP > 400 pg/ml or BNP > 80 pg/ ml)	Aliskiren, valsartan, aliskiren/valsartan or placebo
AVOID (SPP100C2201)	Hypertension and Type 2 diabetes mellitus	Aliskiren or placebo on top of losartan

Data from the completed aliskiren and fixed dose combination clinical trials were pooled into the "Alismart dataset". This dataset includes studies conducted with aliskiren monotherapy and the aliskiren fixed dose combinations with amlodipine, hydrochlorothiazide and valsartan. Studies are divided into those up to 24 weeks exposure short term studies and long term studies lasting longer than 24 weeks. Long term data are limited, with only 1968 patients treated with aliskiren monotherapy in long term studies included into this dataset, 320 of which were diabetic. Data from ALTITUDE are not included in the dataset at this time.

An analysis of these data has been performed to review relevant data for the risks of acute renal failure, cerebrovascular disorders, hypotension, hyperkalaemia, myocardial infarction, Cardiac Failure and Death identified in as defined AEs of interest from the ALTITUDE study. These AEs of interest were analysed in two populations of the dataset – those that are similar to the ALTITUDE patient population (those with diabetes and reduced eGFR at baseline) and those without this baseline medical history.

In short term trials, no differences were observed between groups treated with aliskiren (as monotherapy or in combination with other antihypertensives) and placebo (plus background therapy of other non-aliskiren antihypertensive agents) with regards to defined AEs of interest. Further subgroup analysis did not demonstrate evidence of differential occurrence of defined events of interest in subgroups of ALTITUDE-like population (defined as patients with diabetes and eGFR below 60 mL/min/1.73 m^2) vs non-diabetic patients with normal renal function or between patients treated with or without concomitant ARB/ACE inhibitor. The patient numbers are however low for all defined AEs of interest and the treatment duration is limited (<24 weeks)

In the long term dataset (26 to 52 weeks treatment duration), the rates of defined AEs of interest appear to be higher, although the total number of events is still low, in patients treated with aliskiren plus ACE inhibitors and/ or ARB compared to those treated with aliskiren without an ACE inhibitors or ARB.

Whilst this analysis may indicate a potential higher incidence of the "defined AEs of interest" from the ALTITUDE trial in both patients with diabetes and renal failure compared those without and those treated with an ACE inhibitor/ARB in addition to aliskiren, conclusions may be confounded by the merging together of studies conducted in different patient populations. Additionally, studies that make up the Alismart dataset are of duration <1 year.

It should be noted that ALTITUDE data reported from the Kaplan Meier curves divergences in time-to-event after 1.5 years of follow-up (overall). Therefore, results from short-term studies do not add relevant findings for assessing the benefit-risk profile of aliskiren. In the long term studies very few patients were identified in the ALTITUDE-like population with diabetes and reduced eGFR at baseline. Although such results should be taken cautiously, in the "population without diabetics or decreased renal function", the adverse events of interest appear to occur at slightly higher rates in patients treated with aliskiren plus ACEi and/or an ARB than patients treated with aliskiren without an ACE inhibitor or ARB.

Review of data from ASPIRE study

This study has been considered to be of relevance to aid with interpretation of the ALTITUDE findings.

ASPIRE study

The ASPIRE study was a 36-week, multicenter, randomised, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of aliskiren on the prevention of left ventricular remodeling in high risk post-acute myocardial infarction patients when added to optimized standard therapy including either an ACEi or an ARB. The primary objective of the study was to test whether aliskiren 300 mg, in addition to standard therapy, has superior efficacy compared to placebo in reducing the primary index of adverse cardiac remodeling in patients after high risk acute myocardial infarction.

No difference was observed between aliskiren versus placebo in the change in left ventricular systolic volume. Furthermore, there were no differences in any of the secondary efficacy variables, including the composite of CV death, hospitalization for heart failure or reduction in left ventricular ejection fraction (LVEF) by greater than 6 points, 29 (7%) vs. 24 (6%), HR 1.06 (CI: 0.60, 1.8) p=0.85, or the clinical composite of cardiovascular death, hospitalization for heart failure, recurrent MI, stroke, or resuscitated sudden death, 39 (9%) vs. 34 (9%), HR 1.01 (CI: 0.62, 1.63); p=0.98. All-cause mortality was low for this high-risk MI population. However, it was numerically but not statistically significantly higher in the aliskiren group, 17 (4%) vs. 8 (2%), HR 1.83 (CI: 0.79, 4.3), p=0.16.

There were non-significant numerical imbalances between treatment groups for the individual components including stroke, in the aliskiren treatment group vs. placebo patients [HR 2.97 (CI: 0.59-14.86), p=0.1849]. Considering the fact that the number of stroke events was small (N=9; 1.1%) overall and that the study was neither designed nor powered to show differences in this endpoint, the conclusion at that time was that there was no significant differences between groups.

Furthermore, the number of patients with hypotension, hyperkalaemia or renal dysfunction during the double-blind period was higher in the aliskiren group as compared to the placebo group (26.3% vs. 13.6%, respectively). The total of hyperkalaemia events was 6.2% for aliskiren vs. 1.5% for placebo. The PT of hypotension related events (17.3% for aliskiren vs. 10.3% for placebo) were mainly driven by preferred term of hypotension and dizziness. Renal dysfunction (6.6% for aliskiren vs. 2.8% for placebo) was mainly driven by renal failure, blood creatinine increased, renal impairment and blood urea increased.

The ASPIRE study does not provide information on long term data. The study shows that aliskiren has no effect on Left Ventricular (LV) remodelling while hypotension, hyperkalaemia or renal dysfunction during the double-blind period was higher in the aliskiren group as compared to the placebo group (26.3% vs. 13.6%, respectively).

These results confirm the findings of the ALTITUDE study showing no increase in the occurrence of hospitalisations for heart failure. These data suggest a neutral effect of aliskiren on heart failure/left ventricular dysfunction, indicating no protective effect.

2.2.2. Post marketing data

The last PSUR for aliskiren has recently been submitted to regulatory authorities and covered the one year period from 01 Oct 2010 to 30 Sep 2011 and additionally a review of cumulative data from the date of first launch to 30 September 2011 was also submitted.

The cumulative patient exposure to aliskiren in the post marketing use since launch in March 2007 is estimated to be 1,946,000 patient treatment years.

i. Renal Dysfunction

The cumulative search, which included all clinical trial reports, reports from post marketing surveillance studies and spontaneous reports, identified 852 cases relating to renal impairment, of which 596 were spontaneous reports, 10 were literature reports, 80 clinical trial reports, and 166 were PMS reports. Only 5 of these reports were from the ALTITUDE trial.

Of the 852 reports retrieved, there were two hundred and forty cases reporting preferred terms representing renal failure/renal dysfunction and 84 cases were reported with laboratory abnormalities that were assessed as being consistent with showing renal failure. Five hundred and twenty eight cases were not reported as renal failure or serious renal dysfunction and did not have lab information to suggest such a diagnosis.

Out of the 324 cases with evidence of renal failure/ renal dysfunction, pre-existing renal disease was reported in 47%, diabetes in 32%, age of ≥65 years in 44% of the cases, use of concomitant ACE inhibitors or ARBs in 47%, and concomitant medication with NSAIDs in 16 % of the cases.

Of the 45 clinical trial cases of serious renal impairment/renal failure, 20 cases were suspected by the Investigator to be related to aliskiren.

Given that most events cited in sufficiently documented cases were from patients with pre-existing renal failure or diabetes or were using ACE inhibitors, ARBs or NSAIDs concomitantly, it can be concluded that these risk factors potentially predisposed patients to a higher risk of experiencing renal AEs as compared to those without these risk factors.

ii. Hyperkalaemia

The cumulative search in the latest PSUR identified 358 cases consistent with hyperkalaemia. Of the 264 spontaneous and literature reports, 132 were identified as cases with higher severity and of these 132 cases, 104 were confounded with underlying conditions or with concomitant use of medications known to increase risk of hyperkalaemia.

This cumulative analysis suggests that patients treated with aliskiren and other RAAS blockers or NSAIDs, or those with pre-existing cardiac disease, renal disease or diabetes are at higher risk than general hypertensive population for development of hyperkalaemia. Therefore it was proposed in PSUR 7 to further strengthen the wording to warn of the higher incidence of hyperkalaemia in high risk populations.

iii. Hypotension

The cumulative search in PSUR 7 identified a total of 321 cases of hypotension of which 241 were serious cases.

No specific pattern in time to onset has been identified (58 cases occurred within the first month of treatment, with 44 cases reported between 1-3 months, and 51 cases occurring after the third month of treatment). However, 10 cases were identified as first dose hypotension. The majority of cases defined as “clinically significant” were confounded either by historical/current medical condition or concomitant medications. 12 cases were identified with an event of hypotension that was associated with collapse or syncope or leading to hospitalization, for which an association with aliskiren was not excluded.

Based upon the occurrence of these events of hypotension in patients treated with aliskiren, the proposal to add “hypotension” as an adverse drug reaction has been agreed by the CHMP.

iv. Stroke

The analysis of all relevant post marketing reports identified for aliskiren identified 138 reports with sufficient documentation for further analysis. The majority of these reports represented ischemic stroke as would be expected in a hypertensive patient population. Risk factors in addition to hypertension included diabetes, renal dysfunction and carotid artery stenosis. No specific pattern was observed with regards to the time to onset of occurrence of event.

Stroke is an event that occurs at increased rates in patients with hypertension, atrial fibrillation, diabetics, smokers and those with hyperlipidaemia.

3. Overall discussion and benefit/risk assessment

Safety aspects

i. ALTITUDE study

All the information is based on the interim results of ALTITUDE study which is now terminated.

ALTITUDE was a double-blind placebo-controlled, randomised trial that enrolled patients with Type 2 diabetes and nephropathy of approximately 4 years of duration. Nearly half of the patients also had significant cardiovascular disease. Patients with uncontrolled hypertension were excluded. Aliskiren was tested against placebo when added to standard therapy including an ACE inhibitor (ACEI) or ARB. The composite end point consisted of 5 cardiovascular (CV death, non-fatal MI, non-fatal stroke, resuscitated sudden death and hospitalization for heart failure) and 2 renal components (doubling of serum creatinine, end stage renal disease / renal death). The goal was to demonstrate an overall improvement in cardiovascular and/or renal disease progression and outcomes with aliskiren therapy.

Review of un-blinded data by the data monitoring committee resulted in a recommendation to cease study medication and begin to close the ALTITUDE study. The report concluded that the study was very unlikely to meet its primary efficacy endpoint of demonstrating an improvement in cardiovascular or renal outcomes. The data also showed a higher incidence of adverse outcomes in the aliskiren arm (non-fatal stroke, ESRD/renal death, hyperkalaemia and hypotension) based on 69% of the projected total primary outcome events.

In the overall randomized population, the hazard ratio (aliskiren vs. placebo) for the primary CV or renal composite endpoint is 1.09 (95% CI: 0.97, 1.22, 2-sided p=0.17). This indicates a potential increased risk with aliskiren.

The hazard ratio for the secondary cardiovascular outcome, consisting of the CV components, is 1.14 (95% CI: 0.99, 1.30, 2-sided p=0.07), again suggesting a lack of benefit and potential harm. The hazard ratio for the non-fatal stroke component within the primary outcome is 1.34 (95% CI: 1.01, 1.77, 2-sided p=0.044) with absolute rates of 2.6% (112 events) vs. 2.0% (85 events) in aliskiren and placebo groups respectively.

The hazard ratio (aliskiren vs. placebo) for the secondary renal outcome, consisting of the renal components is 0.93 (95% CI: 0.76, 1.15, 2-sided p=0.52). Though this suggests the possibility of an overall benefit for aliskiren, the result is heavily impacted by the contribution of doubling of serum creatinine, HR 0.90 (95% CI: 0.71, 1.12). Importantly, the observed rates of end stage renal disease / renal death demonstrate a numerical trend against aliskiren with a HR of 1.22 (95% CI: 0.87, 1.72)).

Kaplan Meier curves for the above mentioned composites, as well as stroke, show divergence beginning approximately 1.5 years into the trial.

Although the study was conducted in patients with diabetes, a large proportion of patients had underlying cardiovascular disease and a sizeable proportion of patients did not have renal disease. The incidence of serious cardiovascular events was of relevance in patients with previous cardiovascular disease. Although the HR increased similarly in patients with and without CV events, the absolute risk of CV events on aliskiren was increased versus placebo in patients with previous cardiovascular disease (15.0% and 13.4%, HR =1.12) compared to patients without previous cardiovascular disease (7.0% and 6.1%, HR = 1.16). Among patients with previous CV events, the highest HR was observed in aliskiren-associated resuscitated sudden death (HR 1.64), and lowest HR was associated with unplanned hospitalisation for heart failure HR (HR 0.98). One plausible molecular mechanism underlying the observed increased in CV events is the abrogation, in patients previously treated with ACEis, of the protective bradichinin-medited CV effect of ACEis due to the up-stream blockade of the RAAS pathway by the addition of aliskiren. However the full mechanism of action is still unclear.

Additional sub-analyses were conducted to further understand the above findings. The subgroup analyses are generally consistent with the overall findings regardless of the demographics (age, race, regions), haemodynamics (blood pressure), co-medication, (ACEI, ARB, CCBs, beta-blockers anti-diabetics), or baseline renal parameters (proteinuria, eGFR). No subgroups with a clear benefit or particularly increased risk were identified.

Review of cases of stroke, sudden death, and renal SAEs, showed a numerical excess of events in the aliskiren group compared to placebo in the ALTITUDE study. The absolute risk of developing a CV event is greater in diabetic patients with previous CV events in the aliskiren group and there are concerns on the long-term safety profile of aliskiren in combination with ACEis or ARBs also in non-diabetic patients with a history of cardiovascular events.

Based on the results of the ALTITUDE study the benefit-risk balance for aliskiren when used in diabetic patients or patients with renal impairment receiving ACEis or ARBs is considered negative.

ii. Ad-hoc Expert group meeting

An *ad hoc* expert group on Cardiovascular was consulted and was of the opinion that, the data from ALTITUDE give rise to the concern that the combination with ACE inhibitors or ARBs may increase the risk in subjects with diabetes and renal disease (eGFR < 60 ml/min/1.73 m^2) and/or proteinuria particularly in terms of cerebrovascular and possibly cardiovascular events, hyperkalaemia,

progression to end-stage kidney disease. As this patient population is frequent among the general hypertension population, the group was of the view that the concern regarding the use of the combination should be applied also to the current indication. An oral explanation took place during the meeting and the experts had the opportunity to pose questions to the MAH representatives. Based on the available data from ALTITUDE, the experts were of the view that no group of patients with a positive benefit/risk balance can be identified for this combination treatment in the patient population enrolled in the ALTITUDE study.

The expert group also agreed that the available data suggest that the safety concerns raised for the use of aliskiren in combination with ACE inhibitors or ARBs apply also to non-diabetic subjects with previous cardiovascular disease or with severe renal impairment and these patients should be carefully monitored in clinical practice. The expert group emphasised that all the identified safety concerns will have to be re-evaluated once the complete data set and analyses from ALTITUDE become available.

Based on all the above ALTITUDE study results, analysis of the study data, and the conclusions of the expert group the CHMP agreed that the aliskiren containing products should not be used in combination with ACE inhibitors or ARBs in patients with diabetes mellitus or renal impairment (glomerular filtration rate (GFR) < 60 ml/min/1.73 m^2) and that the combination with ACE inhibitors or ARBs is not recommended in all other hypertensive patients.

iii. Other Studies

Data from completed aliskiren and fixed dose combination clinical trials were pooled into a dataset. This dataset includes studies conducted with aliskiren monotherapy and the aliskiren fixed dose combinations with amlodipine, hydrochlorothiazide and valsartan.

One of the completed studies that the CHMP looked at was the ASPIRE study. The ASPIRE was a 36-week, multicenter, randomised, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of aliskiren on the prevention of left ventricular remodelling in high risk post-acute myocardial infarction patients when added to optimised standard therapy. The primary objective of the study was to test whether aliskiren 300 mg, in addition to standard therapy (ACE inhibitors or ARBs), has superior efficacy compared to placebo in reducing the primary index of adverse cardiac remodelling in patients after high risk acute myocardial infarction. In the ASPIRE study, hypotension, hyperkalaemia or renal dysfunction during the double-blind period was higher in the aliskiren group as compared to the placebo group (26.3% vs. 13.6%, respectively). The total of hyperkalaemia events was 6.2% for aliskiren vs. 1.5% for placebo. Renal dysfunction (6.6% for aliskiren vs. 2.8% for placebo) was mainly driven by renal failure, blood creatinine increased, renal impairment and blood urea increased. The CHMP agreed that the safety results of the ASPIRE study compared to placebo also concur with the safety data of the ALTITUDE study.

There are four additional ongoing aliskiren studies in adult patients. These trials are ATMOSPHERE (SPP100F2301) and ASTRONAUT (SPP100A2368) in chronic and acute heart failure respectively, APOLLO (SPP100G2301) in elderly hypertensive patients and AQUARIUS study (SPP100A2366) in patients with coronary artery disease. The safety results from ALTITUDE were provided to the respective DMCs of these four studies. The DMCs recommended that these on-going studies continue and the CHMP was in agreement.

iv. Postmarketing data

The last submitted PSUR 7 for aliskiren was taken into account for the assessment.

The events in renal dysfunction were from patients with pre-existing renal failure or diabetes or were using ACE inhibitors, ARBs or NSAIDs concomitantly. In that effect it is concluded that these risk factors predisposed patients to a higher risk of experiencing renal adverse events.

In addition the cumulative analysis of hyperkalaemia suggests that patients treated with aliskiren and other RAAS blockers or NSAIDs, or those with pre-existing cardiac disease, renal disease or diabetes are at higher risk than general hypertensive population for development of hyperkalaemia. Therefore it was proposed to further strengthen the warning of the higher incidence of hyperkalaemia in high risk populations.

Hypotension, syncope and stroke were also observed in the post-marketing data especially if combining medicinal products that affect this system. Dual blockade of the renin-angiotensin-aldosterone system (RAAS) by combining aliskiren with an ACEi or an ARB is therefore not recommended.

Increases in serum potassium have been observed with aliskiren in post-marketing experience and these may be exacerbated by concomitant use of other agents acting on the RAAS or by non-steroidal anti-inflammatory drugs (NSAIDs). In particular the cumulative analysis of the post-marketing data in hyperkalaemia confirmed that most cases with serum potassium above 5.5 mmol/ml were observed in patients treated with aliskiren and other RAAS blockers or NSAIDs, or those with pre-existing cardiac disease, renal disease or diabetes are at higher risk than general hypertensive population for development of hyperkalaemia. Therefore it was proposed to further strengthen the warning of the higher incidence of hyperkalaemia in high risk populations. Furthermore the monitoring of the renal function including serum electrolytes (including potassium) is considered necessary in such cases. Consistent with standard medical practice, periodic determination of renal function including serum electrolytes is advised by the CHMP if co-administration is considered necessary.

Taking into account the above frequencies the CHMP recommended that a relevant warning is put in the product information notifying of the possibility of developing the above mentioned adverse events.

Benefit/risk balance

In view of the above data the CHMP agreed that the Benefit-Risk balance of aliskiren containing medicinal products for hypertension remains positive under normal conditions of use, taking into account the restrictions and warnings agreed.

3.1. Risk management plan

At the CHMP for this Article 20 procedure the Risk Management Plan (RMP) has not been requested or discussed. Nevertheless the CHMP recommended that an updated RMP should be submitted by the MAH that adequately describes all the safety concerns, the pharmacovigilance activities and the interventions designed to identify, characterise, prevent or minimise the risks.

3.2. Product information

Following the assessment of all the available data from clinical trials and post-marketing data the Product Information of the aliskiren containing products have been amended to reflect the newly available safety information.

Summary of Product Characteristics (SmPC)

The main amendments have been in the following sections of the SmPC:

Section 4.3 "Contraindications"

The CHMP requested that a contraindication was added against the use of aliskiren in combination with angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) in patients with diabetes mellitus or renal impairment (glomerular filtration rate (GFR) < 60 ml/min).

Section 4.4 "Special Warnings and precautions for use"

The CHMP also recommended the addition of a warning that aliskiren and another RAAS agent should not be used concomitantly in any hypertensive patient.

Furthermore, the incidents of hypotension, stroke, hyperkalaemia, and changes in renal function (including acute renal failure) have been included as those have been reported in monotherapy from the post-marketing observations.

Section 4.5 "Interaction with other medicinal products and other forms of interaction"

The combination of aliskiren with ARBs or ACEi is being contraindicated in patients with diabetes mellitus or renal impairment (eGFR < 60 ml/min/1.73 m^2) and is not recommended in other patients in accordance with the findings of the recent available data.

In addition increases in serum potassium have been observed with aliskiren in post-marketing experience and these may be exacerbated by concomitant use of other agents acting on the RAAS or by non-steroidal anti-inflammatory drugs (NSAIDs). The CHMP recommended that monitoring of renal function including serum electrolytes should be implemented if co-administration aliskiren with of other agents acting on the RAAS or NSAIDs is considered necessary.

Other changes proposed to the SmPC

In addition to the changes summarised above, following further review of the ALTITUDE data and in consideration of the safety profile of aliskiren in post-marketing experience, the safety information in the following sections of the SmPC has been strengthened.

Section 4.2 "Posology"

Information on no adjustment of the initial dose has been added to the posology section in patients with renal impairment. A recommendation not to use aliskiren in patients with severe renal impairment (GFR < 30 mL/min/1.73 m^2) has been added.

Section 4.4 "Special Warnings and precautions for use"

In this section the CHMP recommended the reinforcement of the warning on renally impaired patients for exercising caution when aliskiren is given in the presence of conditions pre-disposing to kidney dysfunction and also reconfirming that the concomitant use of other agents acting on the RAAS in patients with decreased renal function (GFR < 60 ml/min/1.73 m^2) is contraindicated.

Section 4.8 "Undesirable effects"

In this section the adverse events of dizziness and hypotension were added, as well the information on hyperkalaemia (increased serum potassium) with the concomitant use of aliskiren with either RAAS blockers or NSAIDS.

Annex II

- **OBLIGATION TO CONDUCT POST-AUTHORISATION MEASURES**

The MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
The MAH shall submit the final results and study report for the active treatment phase of the ALTITUDE study when available	31 July 2012
The MAH shall submit an updated risk management plan (RMP) that adequately describes all the safety concerns, the pharmacovigilance activities, PASS and the interventions designed to identify, characterise, prevent or minimise the risks.	Within a month following the Commission Decision

Package Leaflet

The relevant sections of the Package Leaflet have been amended to reflect the changes made in the SmPC.

4. Overall conclusion

In conclusion the CHMP reviewed all interim data available from the ALTITUDE study, alongside with all data from other studies and spontaneous reports of suspected adverse drug reactions. These suggested an increased risk of adverse cardiovascular outcomes (hypotension, syncope, stroke, hyperkalaemia) and changes in renal function (including acute renal failure) when aliskiren is combined with ACE inhibitors or ARBs, especially in diabetic patients and those with impaired renal function.

In view of this the CHMP recommended the contraindication of the use of aliskiren containing medicines in combination with ACE inhibitors or ARBs in patients with diabetes mellitus or renal impairment (glomerular filtration rate (GFR) < 60 ml/min).

Taking into account the post-marketing experience the CHMP concluded for all other patient groups that the use of aliskiren in combination with ACE inhibitors or ARBs is not recommended for the overall patient population.

An initial DHPC letter was agreed by the CHMP in December 2011 to inform the healthcare professionals of the termination of the ALTITUDE study and preliminary warnings.

The CHMP also endorsed the sending out of a Dear Healthcare Professional Communications (in February 2012) to communicate the outcome of the present review.

The CHMP also agreed that the MAH should submit the final results of the ALTITUDE study as soon as they are available.

The CHMP recommended the amendment to the terms of the marketing authorisation for aliskiren containing products for which the revised summary of product characteristics, annex II and package leaflet are set out respectively in annexes I, II and IIIB of the opinion.

The scientific conclusions and the grounds for the amendment of the SmPC, Annex II, and package leaflet are set out in Annex IV of the opinion.

5. Conclusion and grounds for the recommendation

Whereas

- The Committee considered the procedure under Article 20 of Regulation (EC) No 726/2004, for aliskiren containing products initiated by the European Commission.
- The Committee considered the interim results of the ALTITUDE study and all available data submitted from clinical trials, and safety databases in relation to the overall risk of the treatment of hypertension of patients with aliskiren in combination with ACE inhibitors or ARBs.
- The Committee agreed that the ALTITUDE study has not yet been finalised. However and in view of this limitation, the Committee concluded that due to the study findings the benefit-risk balance for aliskiren when used in diabetic patients receiving ACE inhibitors or ARBs or patients with renal impairment (GFR < 60 ml/min/1.73 m^2) is considered negative.
- The Committee agreed however, that the results of the ALTITUDE study provided evidence of an increased risk of cardiovascular and renal complications. Considering all the currently available data the Committee considered that it is justified to amend the Product Information for all aliskiren containing medicinal products in the treatment of hypertension in diabetic patients and patients with renal impairment (GFR < 60 ml/min/1.73 m^2). Therefore the combination of aliskiren with ARBs or ACEi is being contraindicated in patients with diabetes mellitus and in patients with decreased renal function. In addition the Committee agreed that dual blockade of the renin-angiotensin-aldosterone system by combining aliskiren with an ACE inhibitors or an ARB is therefore not recommended in all other patients.
- The Committee agreed that increases in serum potassium have been observed with aliskiren in post-marketing experience and these may be exacerbated by concomitant use of other agents acting on the RAAS or by non-steroidal anti-inflammatory drugs (NSAIDs). Therefore the Committee recommends the monitoring of the renal function including serum electrolytes if co-administration is considered necessary.
- The Committee concluded that the benefit-risk balance of Rasilez for hypertension is positive under normal conditions of use, taking into account the restrictions and warnings agreed.

In view of the above, the CHMP has recommended the variation to the terms of the Marketing Authorisation for Rasilez, for which the relevant sections of the Summary of Product Characteristics, Annex II and Package Leaflet are set out in Annex I, Annex II and III B and subject to the conditions set out in Annex II.